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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/526,320	03/15/2000	Dmitry Gabrilovich		9321

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EXAMINER
WEHBE, ANNE MARIE SABRINA

ART UNIT	PAPER NUMBER
1632	10

DATE MAILED: 12/12/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/526,320	Gabrilovich
Examiner	**Art Unit**
Anne Marie Wehbé	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Sep 30, 2002* .

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-11, 15-22, 24, 26-31, 33-37, and 61-135* is/are pending in the application.

4a) Of the above, claim(s) *5-10 and 61-135* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-4, 11, 15-22, 24, 26-31, and 33-37* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *13, 15*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's amendment and response received on 9/30/02 has been entered. Claims 12-14, 23, and 25 have been canceled. Claims 1-11, 15-22, 24, 26-31, 33-37, and 61-135 are pending in the instant application. This application contains claims 5-10 and 61-135 drawn to an invention non-elected without traverse in paper no. 7. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01. Claims 1-4, 11, 15-22, 24, 26-31, and 33-37 are currently under examination in the instant application. An action on the merits follows.

Oath/Declaration

The previous office action stated that the oath or declaration is defective because it does not identify the post office address of each inventor. The office acknowledges that the declaration indicates that the post office address and the residence address is the same. The declaration is therefore considered proper and in compliance with 37 CFR 1.63(c) and 37 CFR 1.76.

Claim Rejections - 35 USC § 112

The rejection of pending claims 1-4, 11, 15-22, 24, 26-31, and 33-37 under 35 U.S.C. 112, first paragraph, for scope of enablement is maintained in part. Applicant's arguments have been fully considered as they pertain to the remaining grounds of rejection but have not been

found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

The applicant's amendments to the claims have overcome the issue raised in previous office actions regarding the lack of enablement for treating "any" hyperproliferative disease. The claims as amended now recite treating a human having cancer or pre-cancerous disease.

The applicants have also amended the claims to limit the species of vector to an adenovirus particle comprising an expression construct. The previous office action stated that the specification did not provide an enabling disclosure for the treatment of cancer by intradermal injection of an adenovirus encoding any tumor suppressor gene, including p53. This issue is maintained. The applicant argues that no evidence has been provided which demonstrates that the skilled artisan could not use the invention as claimed to treat cancer and that examples need not be presented for every embodiment of the invention, *In re Borkowski* . While working examples are not required, ".. the lack of working examples, is, nevertheless, a factor to be considered in a case involving both physiological activity and an undeveloped art. When a patent applicant chooses to forego exemplification and bases utility on broad terminology and general allegations, he runs the risk that unless one with ordinary skill in the art would accept the allegations as obviously valid and correct, the examiner may, properly, ask for evidence to substantiate them". *Ex parte Sudilovsky* (BdPatApp&Int) 21 USPQ2d 1702, citing *In re Novak*, 306 F.2d 924, 134 USPA 335 (CCPA 1962) 4 and *In re Fouche*, 439 F.2d 1237, 169 USPQ 429 (CCPA 1971). Furthermore, in response to the applicant's contention that the office has not provided sufficient

evidence, the applicant is directed the previous office action which provided an analysis of the *ex vivo* working examples presented in the specification, a discussion of the particular problems and the level of unpredictability associated with cancer immunotherapy supported by several prior art references ,and a particular example from the prior art where intradermal immunization with a viral vector encoding p53 did not lead to significant anti-p53 immune responses *in vivo*, see paper no. 12 and Hurpin et al.

The applicant argues that the references previously cited, Verma et al., Orkin et al., and Marshall et al. speak to problems with "optimization" of gene therapy and not "operability", which applicants state is the correct standard for enablement, citing *In re Marzocchi*. Please note that applicant's methods recite the treatment of cancer. Thus, the "operability" of the instant methods rests on whether following the method steps as claimed will actually result in the treatment of cancer in the human host. Verma et al., Orkin et al., and Marshall et al., were cited to establish the state of the art of *in vivo* therapeutic gene delivery at the time of filing. As stated in previous office actions, the combined teachings of Verma et al. Orkin et al., and Marshall et al. demonstrate that at the time of filing, gene therapy of disease was not considered an established and predictable therapeutic strategy for diseases including cancer. The fact that Marshall et al. concludes that "many problems must be solved before gene therapy will be useful for more than the rare application" (Marshall (1995) Science, Vol. 269, page 1054, column 3, paragraph 2, and page 1055, column 1), and Orkin et al. states that," [w]hile the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any

gene therapy protocol" clearly demonstrates that gene therapy was not considered predictably operable at the time of filing. Furthermore, the previous office action cited Hurpin et al. as specific evidence that the intradermal injection of a viral vector, vaccinia virus, encoding p53 is completely ineffective in generating either anti-53 antibodies or CTL (Hurpin et al. (1998) Vaccine, Vol. 16, No. 2/3, 208-215, see page 210, column 2, and page 211, Figure 1). Note in particular that the level of CTL response following intradermal injection of the recombinant vaccinia virus encoding p53 is actually lower than the background response obtained from immunization with empty vector. Applicant's comments in the instant response that Hurpin does not provide sufficient evidence to demonstrate the inoperability of a poxvirus vector or other viral vectors such as adenovirus for generating therapeutic anti-tumor immune responses is particularly confusing in that they contradict applicant's statements in the previous response, paper no. 11, that based on the teachings of Hurpin et al. that intradermal administration of a vaccinia viral vector encoding p53 does not lead to therapeutic anti-tumor immune responses, "one skilled in the art would not expect success generally, much less success using another virus like adenovirus" (see applicant's response received on 4/8/02, page 16). Thus, applicant's original statements of record support the unpredictability of generating anti-tumor immune responses by intradermal injection of adenovirus encoding p53.

In addition, in regards to applicant's *ex vivo* working examples, the previous office action explained that the working examples provided utilize an *ex vivo* approach involving the administration of dendritic cells transduced ex vivo with an adenovirus encoding p53 either i.p,

s.c, or i.v. The applicant's working examples do not utilize the intradermal injection route recited in the instant claims. The prior art of record clearly demonstrates that the route of administration of a viral vector has substantial effects on its ability to generate an immune response against a tumor suppressor gene such as p53 (see Hurpin et al.). Further, the direct administration of a viral vector for the transduction of dendritic cells *in vivo* is affected by the rate of clearance of the vector from the injection site, the tropism of the vector for the target cell, and the rate of cell transduction. Thus, these two methods are not equivalent and a nexus cannot be drawn between applicant's *ex vivo* results and the instant methods of treating cancer by direct intradermal injection of an adenovirus comprising expression constructs. The applicant's instant response has supplied a post-filing publication by Gilbert et al. which demonstrates that an adenovirus encoding the CS gene from Plasmodium berghei is capable of inducing strong CD8+ T cell responses after intradermal injection. The antigen used by Gilbert et al. is a strong parasitic antigen. Pathogenic antigens, such as the CS gene product, are highly antigenic, non-self proteins. During development, mammals develop tolerance towards self-antigens in order to prevent inappropriate and destructive auto-antigen immune responses. As such a nexus cannot be drawn between results obtained using a foreign pathogenic antigen and the applicant's claimed invention which is drawn to immunization with a self antigen. Furthermore, the Gilbert et al. paper teaches away from the instant invention. The Gilbert et al. paper teaches that a single injection of any of the viral vectors or DNA plasmids tested is insufficient to protect mice from parasite challenge despite the fact that significant levels of anti-CS CD8+ T cell responses were present. In fact,

even two injections of adenovirus encoding CS resulted in only 13% protection, which is less than that observed in naive mice (Gilbert et al., page 1042, Table 1). Gilbert et al. teaches that adenovirus encoding CS can be used in combination with another virus or DNA plasmid encoding CS for the generation of protective immune responses. Thus, the skilled artisan would not accept the data of Gilbert et al. as supportive of the enablement of the instant invention as claimed.

It is noted that the applicant has further provided a second post-filing article by Kaiserlain et al., however the applicant's response does not refer to this article or discuss its relevance to the instant invention. It is noted, however, that the Kaiserlian article is primarily directed towards intradermal immunization with plasmid DNA. The only reference to intradermal adenovirus administration is found on page 174 which states that recombinant adenovirus can be administered topically by first tape-stripping the corneal layer of the skin followed by application of the adenovirus by occlusive technique. The specification does not teach these techniques. As stated in *In re Glass*, 181 USPQ 31, (CCPA 1974), if a disclosure is insufficient as of the time it is filed, it cannot be made sufficient, while the application is still pending by later publications which add to the knowledge of the art so that the disclosure, supplemented by such publications, would suffice to enable the practice of the invention. Instead, sufficiency must be judged as of the filing date. The fact that the specific protocols disclosed in Kaiserlian is not disclosed in the specification indicates that the specification does not support the claims as filed, but instead reflects further critical information that is essential for the artisan to practice the invention.

The applicant also argues that the specification is enabling for the use of any and all self-antigens and that the office has not presented sufficient specific evidence to establish a *prima facie* case of non-enablement for the genus of "self-antigens". Please note while applicant's claims broadly recite the intradermal administration of an adenoviral particle comprising an expression construct encoding any self gene, the applicant has elected the species of tumor suppressor genes for examination in the instant application. The claims have not been amended to reflect the elected species or any tumor suppressor gene in particular. Thus, in analyzing the claims as written, the office properly determined whether the instant specification provides an enabling disclosure for the full scope of the claims. The claims as written further read on the administration of a self-gene which may or may not be the same as the self gene product which is altered or increased in the subject. As discussed in detail above, the applicant does not provide any working examples demonstrating intradermal injection of an adenovirus encoding any self-gene including a tumor suppressor. The applicant *ex vivo* working example utilizes p53. The point of the discussion in the previous office actions of the teachings of Vogelstein et al. and Restifo et al. is that in view of the heterogeneity of tumor suppressor and oncogene mutations in a particular tumor cell and the various mechanisms by which tumor cells evade immune responses, the skilled artisan would have considered it unpredictable at the time of filing to treat any type of tumor by generating immune responses according to the instant methodology to any tumor suppressor gene or any other self-gene product. As previously noted, many tumors demonstrate impaired antigen presentation due to loss or down-regulation of MHC, LAMP, proteosome, and antigen expression. The applicant's

claims as amended recite wherein the cancer is characterized by altered or increased expression of the self-gene product. The term altered encompasses both increased or decreased expression , or no expression at all. Immune effector cells identify their targets based on the presence of appropriate forms of the target antigen on the target cell surface. Lack of expression of the target antigen would effectively hide the tumor from any tumor specific immune effector cells. Further, even if the self-gene product is overexpressed, many tumors are incapable or impaired in their ability to appropriately present antigen for immune recognition (Restifo et al.). In addition, the prior art of record teaches the unpredictability of generating immune responses against self-gene products due to the natural development of tolerance to self-antigens in mammals. Thus, for the reasons identified above, the skilled artisan would not have predicted success in treating cancer by intradermal injection of an adenovirus encoding any tumor suppressor gene or self antigen. The applicant is reminded that in *Ex parte Singh*, the court found that the unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991).

The previous office action also raised the following issue: the specification does not provide sufficient guidance for the targeted transduction of dendritic cells following intradermal administration of either viral or non-viral vectors. At the time of filing , the skilled artisan did not consider the targeting of vectors to specific cell types *in vivo* to be predictable . Deonarain, in a review entitled, " Ligand-targeted receptor-mediated vectors for gene delivery", teaches that one of the main obstacles to successful gene therapy is, " ... the ability to target a gene to a significant

population of cells and express it at adequate levels for a long enough period of time", and states that, " .. even after almost 30 years of relentless pursuit, nothing has yet delivered such a promise in terms of clinical results" (Deonarain et al. (1998) Exp. Opin. Ther. Patents, Vol. 8 (1), page 53, lines 1-4, and page 54, lines 12-15). Miller et al. concurs, teaching that the development of surface targeting has been problematic and that the biggest challenge in targeted vector design is to combine targeting with efficiency of gene expression, since , " attainment of one usually compromises the other" (Miller et al. (1995) FASEB, Vol. 9, page 198, paragraph 2). The specification does not provide guidance in the form of detailed teachings or specific working examples for methods to target any vector to dendritic cells or any other cell type *in vivo*. Therefore, in view of the art recognized unpredictability in achieving targeted gene delivery *in vivo* using vectors currently available at the time of filing and the absence of guidance for methods for the targeted transduction of dendritic cells using viral or plasmid vectors *in vivo*, it would have required undue experimentation to practice the instant invention as claimed. The applicant has not addressed this issue.

Finally, it is noted that the present and previous office actions have analyzed the specification in direct accordance to the factors outlined in *In re Wands*, namely 1) the nature of the invention, 2) the state of the prior art, 3) the predictability of the art, 4) the amount of direction or guidance present, and 5) the presence or absence of working examples, and presented detailed scientific reasons supported by publications from the prior art for the finding of lack of enablement for the scope of the instant methods. The analysis and discussion presented in the

present and previous office actions specifically explains why applicant's disclosure does not reasonably correlate with the scope of the claims as written. Furthermore, the applicant is reminded that since, in patentability context, claims are to be given their broadest reasonable interpretations, limitations are not to be read into claims from the specification. *In re Van Guens*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Ultimately, case law states that ".. the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not to find out how to use it for themselves." *In re Gardner* 166 USPQ 138 (CCPA) 1970. Based on the lack of guidance provided by the specification for the full scope of applicant's claims, and the lack of reasonable correlation between the subject matter found to be enabled and the breadth of the claims, it would have required undue experimentation to practice the scope of applicant's invention.

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Thurs and every other Friday from 9:30-7:00. If the examiner is not available, the examiner's supervisor, Deborah Reynolds, can be reached at (703) 305-4051. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The technology center fax number is (703) 308-4242, the examiner's direct fax number is (703) 746-7024.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER